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【 CASE REPORT 】

Diagnosis of Suspected Small Bowel Bleeding by Capsule Endoscopy in Patients with COVID-19

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Abstract:
The current study evaluated the application of small-bowel capsule endoscopy (SBCE) in SARS-CoV-2-infected patients with suspected small bowel bleeding. We analyzed the clinical characteristics, SBCE procedures, examination results, and treatment for cases of suspected small bowel bleeding in two patients with critical COVID-19. SBCE showed active spotting bleeding in the jejunum and ileum with no identifiable lesions in case 1, while multiple small bowel ulcers were detected in case 2. Two patients had relevant changes in their management plans and received specific treatment based on SBCE findings. In summary, SBCE proved to be a non-invasive diagnostic tool for critical COVID-19 patients with suspected small bowel bleeding.

Key words: COVID-19, small-bowel capsule endoscopy, suspected small bowel bleeding

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), has become widespread in China and other countries around the world (1-5). As of March 12, 2021, there were more than 118 million confirmed infections and more than 2.63 million deaths worldwide according to data from Johns Hopkins University.

The most common symptoms of COVID-19 are a fever and cough, but several studies have reported that patients may have gastrointestinal symptoms prior to respiratory symptoms developing (6, 7). Detection of SARS-CoV-2 nucleic acid in the feces of confirmed patients even after viral clearance in respiratory tract suggest that the digestive system may be a potential transmission route and target of SARS-CoV-2 (8-10). Diarrhea, anorexia, and nausea are the most common gastrointestinal symptoms in patients with COVID-19, and severe cases may develop gastrointestinal bleeding (6, 8, 11). In our hospital, two patients with critical COVID-19 underwent small-bowel capsule endoscopy (SBCE) due to suspected small bowel bleeding.

We herein report the clinical characteristics, SBCE procedures, examination results, and treatment for small bowel bleeding in these two patients.

Case Reports

Patients

From January 2020 to June 2020, 7.62% of COVID-19 patients (8/105) developed gastrointestinal bleeding in our hospital, including 2 who had persistent bleeding of unknown origin after gastroscopy and colonoscopy. Therefore, SBCE was performed to detect the focus of the suspected small bowel bleeding. Detection of SARS-CoV-2 ribonucleic acid (RNA) in the specimens of pharyngeal swab and sputum by previously reported real-time reverse transcription polymerase chain reaction (RT-PCR) was used to confirm SARS-CoV-2 infection (12).

The diagnosis of COVID-19 was made according to the protocol for the prevention and control of COVID-19 (in Chinese) issued by the National Health Commission of the People's Republic of China. The study was approved by the medical ethics committee of our hospital. Written informed

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consent was obtained from each patient.

SBCE Procedure

An OMOM capsule system (Jinshan, Chongqing, China) was used in our study. Two patients were deprived of enteral nutrition for more than 72 hours due to active bleeding, and they did not take laxatives for bowel preparation. They were unable to swallow due to endotracheal intubation and mechanical ventilation caused by respiratory failure, so the capsule was introduced into the descending part of the duodenum with endoscopic-assisted delivery through a polypectomy snare. During the examination, intestinal motility was affected because the patients were confined to their bed, and drugs that slowed down gastrointestinal motility, such as somatostatin analogs, had been discontinued. The operators were able to view and analyze the images collected by the camera in real time through the data recorder. Each SBCE device ran for 10 to 11 hours until the battery was exhausted. The imaging data captured by the capsule were subsequently downloaded to an OMOM workstation for storage and a later analysis.

Data Extraction

Two experienced gastroenterologists independently reviewed the capsule video and made a diagnosis. If a discrepancy existed between the two gastroenterologists, the video was retrieved and reevaluated. Data collected included the epidemiological history, demographic and clinical characteristics, prior endoscopic evaluation, prior radiographic evaluation, diagnosis of SBCE, quality of small-bowel mucosal visualization, completion rate, complication of SBCE and interventions after SBCE (reexamination and/or treatment).

Results

Case 1

A 91-year-old man who developed a fever for 4 days was diagnosed with COVID-19. Although he has not been to Hubei Province or been in contact with confirmed patients, he had gone shopping without a mask 10 days before onset of illness. He developed respiratory failure and renal failure during hospitalization. His symptoms of COVID-19 were classified as characteristic of the critical type. Therefore, he was transferred to the intensive-care unit (ICU) and treated with extracorporeal membrane oxygenation (ECMO) and continuous blood purification. The use of heparin was unavoidable during ECMO cannulation and the ECMO run. In addition, the patient received antiviral, antibiotic and glucocorticoid treatment (arbidol 200 mg 3 times per day, favipiravir 600 mg 3 times per day, piperacillin sodium and tazobactam sodium 4.5 g every 8 hours, and methylprednisolone 40 mg per day). One month after admission, the patient developed melena and hemodynamic instability.

Laboratory findings showed a low hemoglobin level of 6.1 mg/dL and abnormal coagulation profiles (platelet count of 20,000/mm^3, international normalized ratio of 1.45, and activated partial thromboplastin time of 114.3 seconds). Abdominal CT showed gallbladder wall thickening and no obvious gastrointestinal neoplastic lesions. CT of the brain and chest, and lower extremity ultrasound were also performed, demonstrating no evidence of ischemia or thrombosis in the corresponding organs. Subsequent digital subtraction angiography (DSA) for the abdominal aorta and mesenteric artery did not reveal the source of the bleeding.

Furthermore, he was subjected to gastroscopy and colonoscopy in a negative pressure room. Gastroscopy showed multiple erosions of the duodenal mucosa combined with oozing, and clips were used to clamp the erosions. Colonoscopy showed multiple polyps in the colon without evidence of active bleeding, but the mucosal visualization obtained for colonoscopy was fair. After gastroscopy treatment, the patient still had repeated melena accompanied by hemoglobin decline. Therefore, SBCE was performed to find the focus of the bleeding.

The mucosal visualization obtained for SBCE was fair in the patient. SBCE revealed no blood in the duodenum and upper jejunum and a small amount of fresh spotting bleeding from the middle and lower jejunum to the middle ileum (Fig. 1), some of which had coagulated into fresh blood clots (Fig. 2). SBCE did not show ulcerated lesions or neoplastic lesions in the small bowel. It also failed to achieve complete small-bowel visualization due to the slow intestinal movement, and the capsule was discharged normally from the body. There were no SBCE-related complications.

According to the results of SBCE, small intestinal angiodysplasia was first considered as the main cause of melena. The risk factors that might lead to bleeding were resolved, including the discontinuation of glucocorticoids and anticoagulants. The patient was treated with somatostatin analogues in combination with supplementation of platelets, fresh-frozen plasma, cryoprecipitate and fibrinogen. After the above treatment, the patient recovered gradually with stable hemoglobin level and no more symptoms of melena. Although sputum and fecal samples turned RNA-negative one month after admission, the patient had extensive lung lesions and required ECMO support for a long time. Accordingly, he was unable to avoid the use of heparin again, and he developed hemorrhaging again one month later. Eventually, the patient died of multi-organ failure three weeks after gastrointestinal rebleeding.

Case 2

An 83-year-old woman with a persistent fever for four days was diagnosed with COVID-19. She had been in close contact with a confirmed patient. She developed respiratory failure and required intubation and invasive mechanical ventilation. Her symptoms of COVID-19 were classified as the critical type. She received concomitant treatment with antivirals, antibiotics and glucocorticoids (arbidol 200 mg 3 times per day, favipiravir 600 mg 3 times per day, imipenem and cilastatin sodium 500 mg every 8 hours, and methylprednisolone 40 mg per day). Twelve days after entering the ICU, the patient developed repeated hematochezia with a signifi-

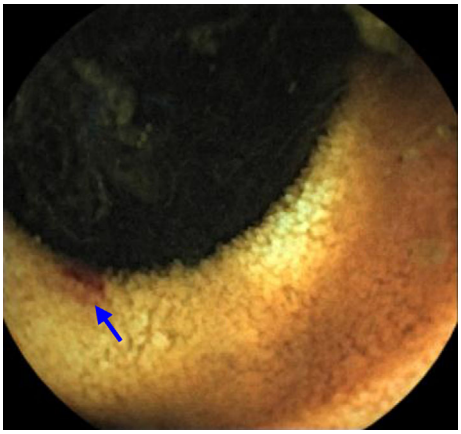

Figure 1. **Images of capsule endoscopy: fresh spotting bleeding in the jejunum. The arrow indicates fresh spotting bleeding.**

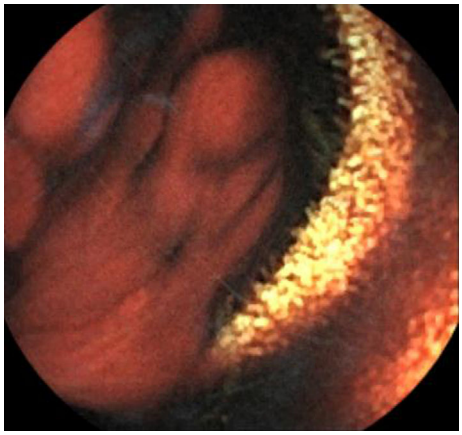

Figure 2. **Images of capsule endoscopy: fresh blood clots in the jejunum.**

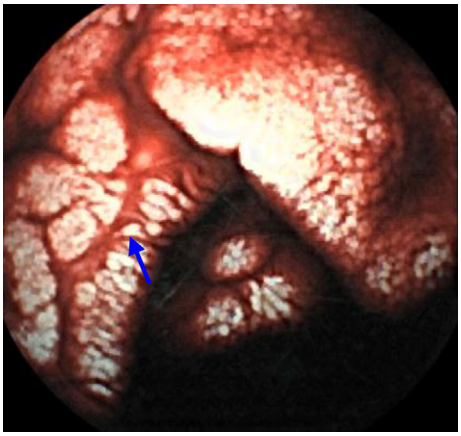

Figure 3. **Images of capsule endoscopy: irregular ulcers in the jejunum. The arrow indicates an irregular ulcer.**

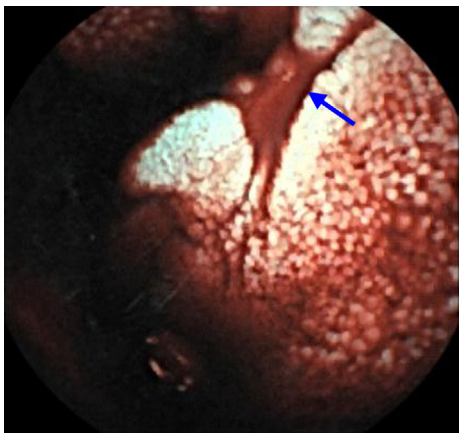

Figure 4. **Images of capsule endoscopy: bleeding from jejunal ulcer. The arrow indicates the location of the bleeding ulcer.**

cant decrease in hemoglobin.

Laboratory tests revealed a low hemoglobin level of 5.5 mg/dL and abnormal coagulation profiles (platelet count of 35,000/mm^3, international normalized ratio of 2.39, and activated partial thromboplastin time of 78.8 seconds). Abdominal CT as well as DSA for the abdominal aorta and mesenteric artery revealed no obvious abnormalities. Chest CT, brain CT, CT pulmonary angiography and lower extremity ultrasound were also performed, demonstrating no evidence of ischemia or thrombosis in corresponding organs.

Furthermore, she was subjected to gastroscopy and colonoscopy in a negative-pressure room. Gastroscopy showed multiple erosions in descending duodenum, and colonoscopy showed normal colorectal mucosa. The patient still suffered from repeated hematochezia after clamping of the erosions with clips. There was no adequate explanation for the hematochezia. Therefore, SBCE was performed to locate the focus of the bleeding.

The mucosal visualization for SBCE was fair in the patient. SBCE revealed a lot of fresh blood in the duodenal lumen. Furthermore, there were many irregular ulcers in the jejunum (Fig. 3), some of which were bleeding (Fig. 4). SBCE took 10 hours and 45 minutes to reach the mid-ileum but did not pass through the ileocecal valve during working hours. SBCE failed to achieve complete small-bowel visualization due to slow intestinal movement, and then the capsule was discharged normally from the body. There were no SBCE-related complications.

Although the duodenal mucosa could not be clearly identified due to the large amount of fresh blood, the locations of bleeding were the duodenum and jejunum, and multiple jejunal ulcers were one of the causes of hematochezia. Subsequent treatment included the application of somatostatin analogues and mucosal protectants, discontinuation of glucocorticoids, and supplementation of fresh-frozen plasma and fibrinogen. After the above treatment, the patient still suffered from repeated fresh bloody stool with a declining hemoglobin level, so double-balloon enteroscopy was conducted, which revealed multiple erosions and superficial ulcers in the descending and horizontal parts of the duodenum and upper part of the jejunum without any evidence of active bleeding.

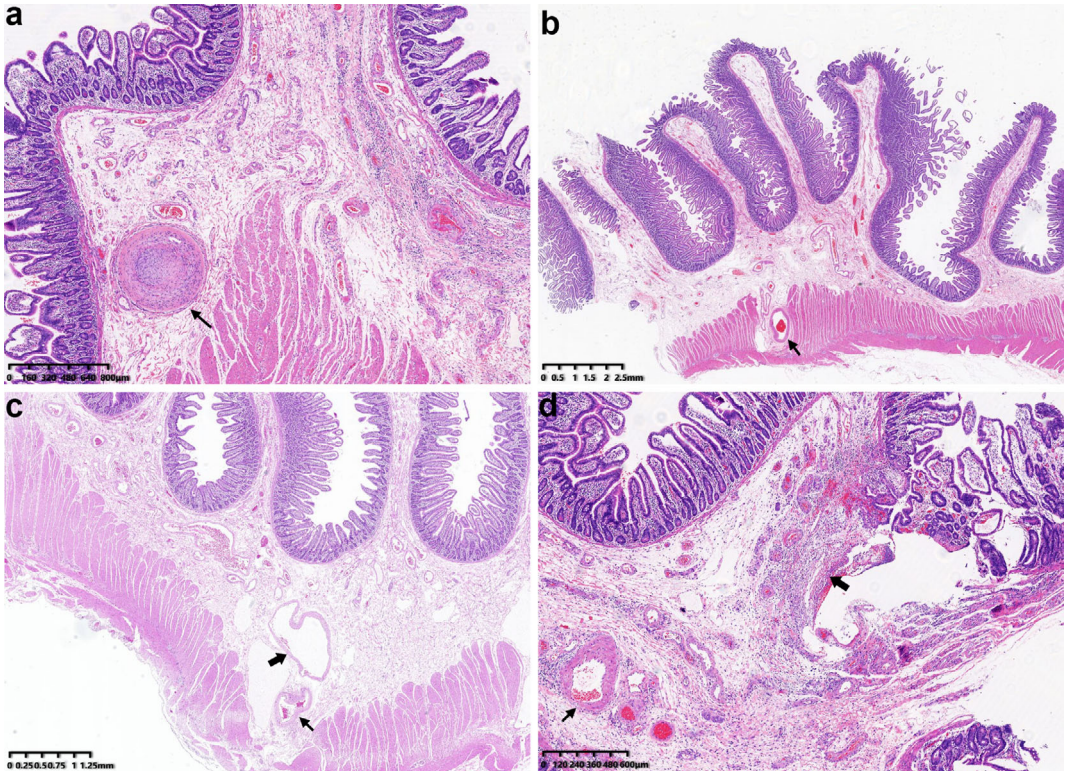

Figure 5. **Pathological findings in intestinal specimens. (a) A Dieulafoy's lesion with evidence of thrombi (arrow) was found in the submucosa. (b) A Dieulafoy's lesion (arrow) was found in the muscularis. (c) A Dieulafoy's lesion (thin arrow) and a dilated thick-walled venule (thick arrow) were found in the submucosa. (d) The thin arrow indicates a Dieulafoy's lesion in the submucosa, and the thick arrow indicates a deep ulcer whose base contained inflammatory exudate and granulation tissue.**

In addition, the patient received surgical treatment because of subsequent hypotension and hemorrhagic shock. During the surgery, multiple ulcers were found in the ascending duodenum and jejunum, some of which were deep and accompanied by bleeding, and the corresponding intestinal segments were excised. The histologic report showed thrombotically occluded arterioles and dilated thick-walled venules in the submucosa and multifocal erosion and ulceration in the duodenum and jejunum. Of note, a dilated submucosal vessel with thrombi and fibrinoid necrosis, also known as Dieulafoy's lesion, protruded through the overlying mucosa (Fig. 5). Furthermore, an immunohistochemical analysis of SARS-CoV-2 (SARS-CoV-2 nucleocapsid antibody, rabbit monoclonal, Sino Biological, Beijing, China, at a 1/200 dilution) in the resected intestinal specimens was negative. After surgery, the patient never developed hematochezia again, and her hemoglobin level remained stable during the six-month follow-up.

Discussion

The diagnosis and management of small bowel bleeding remains difficult because of the limitations associated with routine examination, even in patients without comorbidities (13, 14). It is exceedingly challenging to identify the source of small bowel bleeding in patients with COVID-19. SBCE is a non-invasive, painless, simple and effective examination for the entire small bowel, especially for patients with a poor general condition. SBCE is the first-line diagnostic tool recommended by different medical societies in cases with gastrointestinal bleeding of unknown origin after negative endoscopic findings (15-19). To our knowledge, the present study is the first retrospective study investigating the application of SBCE in SARS-CoV-2-infected patients suspected of having small bowel bleeding.

In the present study, the SBCE procedure performed in our patients with critical COVID-19 was significantly different from that performed in the average patient. First, patients with critical COVID-19 were unable to swallow because they were unconscious, so the capsules were placed in the duodenum by endoscopic-assisted delivery. Second, the intestinal motility of patients with critical COVID-19 was worse than that of the average patient due to their disease, and they were unable to promote small-bowel movement through exercise. Although somatostatin analogs, which affect the intestinal motility, were discontinued, the capsule in both patients only moved as far as the middle ileum during working hours. Third, due to active bleeding and pneumonia, our patients were unable to imbibe a large volume of solution for bowel preparation, which affected the small-

bowel mucosal visualization. However, the bowel visibility in both patients was moderate owing to the discontinuation of enteral nutrition for more than 72 hours. Despite the above difficulties, SBCE is still a safe, convenient and effective option for evaluating SARS-CoV-2-infected patients suspected of having small bowel bleeding.

According to previous studies, the most common causes of suspected small bowel bleeding detected by SBCE were vascular lesions, ulcerative/erosive lesions and small bowel tumors (20-22). In the present study, SBCE showed active spotting bleeding with no identifiable lesions in case 1, so angiodysplasia in the small bowel was first considered as the cause of melena. Old age, the use of anticoagulants and glucocorticoids and the hypoxic-ischemic state caused by COVID-19 may be important risk factors for bleeding of angiodysplasia. Multiple small bowel ulcers were the cause of hematochezia in case 2. Possible causes of small bowel ulcer included hypoxic-ischemic mucosal injury, SARS-CoV-2-induced mucosal injury, stress ulcers and the application of medications known to cause nonspecific ulcerations during the treatment of pneumonia. Our findings provide strong evidence that SBCE can rule out possible conditions and be used to diagnose suspected small bowel bleeding in patients with critical COVID-19.

The question that remains to be discussed is the possible mechanism underlying intestinal mucosal injury in COVID-19 patients. Intestinal hypoxic-ischemic injury in critical COVID-19 patients has been linked to coagulopathy and vasculopathy caused by SARS-CoV-2 (23, 24), which eventually results in an increased rate of small intestinal ulceration and vascular malformation bleeding. Recent studies have reported small bowel ischemia caused by multifocal microthrombi and mesenteric arterial or venous thromboembolism in several patients with severe forms of COVID-19 (23, 25, 26). Likewise, the pathological findings in the present study showed thrombotically occluded arterioles in the submucosa of small intestine. Furthermore, SARS-CoV-2 might enter small intestinal enterocytes through the angiotensin-converting enzyme 2 (ACE2) receptor and then replicate and trigger inflammatory responses (27, 28). Direct tissue damage caused by viral infection of intestine has been reported (29). However, SARS-CoV-2 was not detected in resected intestinal specimens in the present study. It is possible that SARS-CoV-2 did not infect the small intestinal enterocytes, and the patient's small bowel bleeding was instead induced by causes other than the virus infection. Another possibility is that virus-positive small intestinal enterocytes might turn negative just a few days later, since surgical resection of the small bowel lesions occurred two months after the onset of COVID-19, when both sputum and fecal samples were negative for viral RNA.

In the management of small bowel bleeding in patients with critical COVID-19, the first step is to improve the overall condition of the patients and reduce or prevent drug-induced mucosal damage and coagulation dysfunction. It should be noted that the use of ECMO and a ventilator in critical COVID-19 patients may result in gastrointestinal bleeding. The bleeding in EMCO-supported patients may be due in part to the required high doses of heparin, mechanically high blood flow rates and circuit-induced coagulopathy (30-32). These patients may have a high incidence of bleeding despite the use of acid-suppressing agents. The next treatment options depend on the location, cause, and extent of the bleeding. If endoscopic treatment is ineffective or very difficult, surgery may be considered. However, case 1 was unable to stop anticoagulants for a long time because of ECMO support and could not tolerate further surgical exploration due to a poor general condition, which ultimately resulted in an unfavorable outcome.

Several limitations associated with the present study warrant mention. First, the study included only two cases from a single hospital, so the reliability of the conclusion presented here is clearly low. Second, the lack of bowel preparation and poor bowel motility affected the image quality and completion rate of SBCE. Third, the small-bowel mucosa was not tested for viral RNA by real-time RT-PCR. Lin et al. reported that the presence of SARS-CoV-2 in gastrointestinal tissue generally indicated severe gastrointestinal symptoms (6). Further research is needed to identify the relationship between the viral load in the intestinal mucosa and small-bowel lesions.

Conclusion

In summary, SBCE has an established role in the diagnosis of suspected small bowel bleeding for patients with COVID-19. Despite differences in the SBCE procedure being required due to the contagiousness of SARS-CoV-2, SBCE can still help guide clinicians in decision-making concerning subsequent interventions.

Written informed consent was obtained from each patient.

The authors state that they have no Conflict of Interest (COI).

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